

REMARKS

Claims 1-60 are pending. Claims 14, 27, and 60 have been withdrawn from consideration. Claims 1, 15, 28-29, 37, and 49 are the sole independent claims. Applicants believe that amendments to the claims are unwarranted in view of the outstanding rejections.

The rejection of claims 1-13, 15-26, and 28-59 under 35 U.S.C. § 103(a) over U.S. Patent No. 6,506,767 (hereafter "Schumacher") is respectfully traversed.

Applicants believe that the rejection over Schumacher is improper and should be withdrawn upon consideration of the following remarks.

Claim 1 is directed to a pharmaceutical composition of desloratadine comprising of a mixture of crystalline form desloratadine I and II in a weight to weight ratio of **about 25% to about 75% of either form** to the other and a pharmaceutically acceptable excipient.

Claim 15 is directed to a pharmaceutical composition of desloratadine comprising of crystalline form desloratadine I and II in a weight to weight ratio of **about 20% to about 40% of Form II** and a pharmaceutically acceptable excipient.

Claim 28 is directed to a stable mixture of crystalline form desloratadine I and II in a weight to weight ratio of **about 25% to about 75% of either form** to the other, wherein the mixture is stable in that it undergoes less than about 10% polymorphic change for each polymorph after storage for 2 months at 40°C at 75% RH.

Claim 29 is directed to a stable mixture of crystalline form desloratadine in a weight to weight ratio of from **about 20-40% Form II to about 60-80% Form I**, wherein the mixture is stable in that it undergoes less than about 10% polymorphic change for each polymorph after storage for 2 months at 40°C at 75% RH.

Claim 37 is directed to **a mixture of crystalline form desloratadine I and II in a weight to weight ratio of about 25% to about 75% of either form**, prepared by a process comprising: i) combining desloratadine salt, toluene and a base to obtain a reaction mixture; j) heating the mixture, whereby two phases are obtained; k) separating the phases; l) concentrating

the separated organic phase; m) dissolving the obtained concentrate in a toluene-2-propanol mixture containing less than about 20% 2-propanol by volume; n) cooling the solution to obtain a slurry; o) combining the slurry with cold n-heptane; and p) recovering mixture of desloratadine forms I and II.

Claim 49 is directed to a pharmaceutical composition of desloratadine **prepared by a process** comprising the steps of: a) preparing a mixture of crystalline form desloratadine I and II in a weight to weight ratio of **about 20% to about 40% Form II to Form I**; and b) combining the mixture with a pharmaceutically acceptable excipient to obtain a pharmaceutical composition.

Reasons in Support of Nonobviousness

Claims 1, 14, 28-29, 37, and 49 are not obvious over Schumacher because:

- (1) The polymorphic mixture ranges disclosed in Schumacher do not overlap with the presently claimed polymorphic mixture ranges.
- (2) The presently claimed polymorphic mixture exhibits unexpected properties. A careful reading of Schumacher reveals that Schumacher predicts that variable polymorphic mixtures would have variable physical properties. Applicants' claimed desloratadine polymorphic composition possesses substantially constant physical properties, and so contradicts Schumacher's prediction. Given that the polymorphism phenomenon is generally unpredictable, Applicants believe that the observed properties for the claimed compositions represent a result that is unexpected in kind rather than degree.
- (3) Schumacher expressly teaches away from the presently claimed invention, and so one of ordinary skill would not be motivated to prepare or to use the claimed desloratadine mixtures, either alone or in a pharmaceutical composition.
- (4) Schumacher does not disclose a process for preparing the presently claimed crystalline desloratadine polymorphic mixtures.

In view of these considerations, Applicants kindly request allowance of claims 1, 14, 28-29, 37, and 49, as well as their respective dependent claims.

Schumacher does not disclose or suggest the claimed crystalline desloratadine mixtures

Schumacher discloses the preparation of crystalline desloratadine by dissolving desloratadine in a single crystallization solvent to obtain a desloratadine solution, cooling the desloratadine solution so as to obtain crystalline desloratadine (see Exs. 1-5, cols. 10-12). The crystalline desloratadine obtained by the exemplified embodiments contains either a single polymorphic form (Exs. 1-3, Form I and Ex. 4, Form II) or a mixture of polymorphic forms (Ex. 5, $92 \pm 5\%$ Form II). Although Schumacher discloses a mixture of polymorphic forms, Schumacher expressly discloses that "the mixture" is limited to be either a mixture containing at least 99% Form I or a mixture containing at least 85% Form II (see col. 3, lines 53ff). Because the compositional polymorphic ranges disclosed in Schumacher do not overlap with the compositional polymorphic range recited in each of the independent claims, Schumacher does not render these claims obvious.

Applicants' claimed desloratadine is unexpected in view of Schumacher

Expectation: Variable polymorphic mixtures possess variable properties

Because there is no overlap between the ranges disclosed in Schumacher and those recited in claim 1, the next line of analysis is whether the ranges "are close enough that one skilled in the art would have expected them to have the same properties" (see MPEP 2144.05(I)).¹ Applicants note that a careful reading of Schumacher reveals that one would expect that the presently claimed crystalline desloratadine polymorphic mixtures would have variable physical properties, as evidenced by the passage found at column 4, lines 5-11, which recites:

We have discovered that [desloratadine] exists as a mixture of polymorphs. Such a mixture could lead to production of a [desloratadine] product which would exist as a variable mixture of variable composition (i.e., variable

¹ Applicants note that consideration of this line of reasoning should by no means be considered to be an admission that the presently claimed polymorphic range is "close" to the polymorphic range disclosed in Schumacher.

percent amounts of polymorphs) having variable physical properties, a situation unacceptable in view of stringent GMP requirements.

In other words, Schumacher discloses that one would expect that crystalline desloratadine containing a mixture of polymorphs would have "variable physical properties."

Applicants note that results disclosed in the present application reveal quite unexpectedly that the claimed compositions possess substantially constant physical properties. Inspection of the stability tests of Examples 2-4 show that polymorphic change for each polymorph after storage for 2 months at 40°C at 75% RH is less than about 10% (see Applicants' specification at pp. 17-18. This data is reproduced in the following Table.

Time	40°C, 75% RH					
	Ex 2		Ex 3		Ex 4	
	Form I	Form II	Form I	Form II	Form I	Form II
0 week	62	38	74	26	76	24
1 week	63	37	77	23	76	24
2 week	64	36	81	19	82	18
1 month	65	35	78	22	88	12
2 month	65	35	78	22	85	15
3 month	—	—	75	25	82	18
6 month	—	—	75	25	82	18

The Table includes the average percentage of each crystalline form over the reported period of time. As can be seen from the Table, stable mixtures were obtained even though the crystalline forms are not as "pure" as that prescribed by Schumacher. The Office is reminded that Schumacher discloses that it is unacceptable to have "variable percent amounts of polymorphs" since these variable compositions would have "variable physical properties," which is "a situation unacceptable in view of stringent GMP requirements" (see Schumacher at col. 4, lines 5-11). Yet, Applicants' disclosure at page 13, line 29 – page 14, line 26, discloses that, with emphasis added:

Stability of desloratadine at relative humidities of 60% 80% and 100% RH, stability under grinding, thermal stability/melting point in the DSC was monitored. The *stable mixtures* of 25:75, 50:50, 75:25, 84:16 (Form 1:Form 2) *do not show any substantial change* (Chemical: by degradation; Physical: by transformation to another polymorphic form) in

the XRD pattern after exposure at 60%, 80%, 100% RH for one week. Also those *stable mixtures do not show any substantial change in the XRD pattern after grinding for one minute*; The sample is ground by hand in a mortar and pestle for about 1 minute. The separate polymorphs (Form I and Form II) were also monitored as a reference, and shown to be stable as well. *The mixtures also show a substantial lack in chemical decomposition after storage at 100% humidity for one week and after grinding for 1 minute. This lack of decomposition is preferably undetectable by XRD and NMT 3%, more preferably NMT 2%, and most preferably NMT 3% by weight.*

The physical properties of the two separate polymorphs (Form I and Form II) were compared to the physical properties of some mixtures (25:75, 50:50, 75:25, 84:16 Form I:Form II). It was discovered that *polymorphic mixtures with different polymorphic compositions have practically invariable physical properties as compared to the separate polymorphs (Form I and Form II). Hence, even if there is polymorphic transformation, the thermal characteristics of the polymorphic mixture may retain substantially the same*, which is ideal for formulation.

The thermal stability of the mixtures of polymorphs is comparable to that of the separate polymorphs. The melting temperatures of the stable mixtures, as determined in the DSC, is in the range of 157-158°C, while the separate polymorphs give in the DSC melting temperatures of 156°C and 158°C for Form II and Form I respectively. The similarity in melting points of the separate polymorphs and *the stable mixtures indicates that the physical properties are not altered significantly*. The DSC curves of the separate polymorphs also do not show any exotherm of decomposition at the temperature above the melting temperature, and also the stable mixtures do not show any event of decomposition above the melting temperature. This lack of decomposition indicates that *the mixtures like the separate polymorphs are substantially thermally stable*.

In other words, Applicants have shown that mixtures of desloratadine possess substantially constant physical properties. This information is unexpected when one considers the mandate of Schumacher, i.e., that variable compositions have variable physical properties. Because the claimed compositions of desloratadine polymorphic mixtures exhibit properties that are unlike the properties of desloratadine polymorphic mixtures suggested by Schumacher, Applicants believe that the presently claimed compositions are unobvious over Schumacher.

Polymorphism is generally recognized as being unpredictable

Applicants also note that the scientific community as a whole finds that polymorphism to be rather unpredictable. Given this unpredictability, Applicants note that the observed results are even more unexpected. Applicants have cited a number of references that clearly show that the polymorphism phenomenon is unpredictable; excerpts of these references include:

- (1) Byrn et al. Chem. Mater. 1994, 6, 1148-1158 at page 1148, col. 2, 2d full para:
Perhaps the chief challenge in managing the phenomenon of multiple solid forms of drugs is our inability to predict how many forms can be expected in a given case...
- (2) "Polymorphism in Molecular Crystals" Bernstein, J. at page 9, Clarendon Press (2002):
The possibility of polymorphism may exist for any particular compound, but the conditions required to prepare as yet unknown polymorphs are by no means obvious.
- (3) "Solid state Chemistry of Drugs" Byrn S.R., p. 7, lines 1-3, Academic Press (1982):
No rules exist that allow prediction of whether a compound will exhibit polymorphism;...
- (4) "Polymorphism in Pharmaceutical Solids" Brittain, H.G. p. 185, Marcel Dekker (1999):
Until that time [that computer programs are able to predict stable crystal forms] the development scientist is handicapped in attempting to predict how any solid forms of a drug are likely to be found.
- (5) Although general techniques for preparing polymorphic forms are known, there is no accurate way to determine that a particular isolation technique will produce an amorphous or crystalline form. The U.S. Patent Office recognizes the novelty and nonobviousness of polymorphic forms of a compound over previously known forms. See, e.g., U.S. Patent Nos. 4,721,723 (pareoxetine hydrochloride hemihydrate); 6,060,494 (leflunomide); 5,556,839 (dirithromycin); and 5,736,541 (olanzapine).

Schumacher teaches away from the claimed invention

Applicants' specification at page 4, lines 4-8, discloses that:

Schumacher warns against using polymorphic mixtures of desloratadine for formulation. According to Schumacher, "such a mixture could lead to production of [desloratadine] which would exist as a variable mixture of variable composition (i.e., variable percent amounts of polymorphs) having variable physical properties, a situation unacceptable in view of stringent GMP requirements.

Applicants view this warning as an express *teaching away* of the presently claimed subject matter. In this regard, Applicants direct the Examiner to consider the *KSR Court* opinion in its discussion of a *Graham* companion case *U.S. v. Adams*, which recites in part with emphasis added:

[The Court] nevertheless rejected the Government's claim that Adams's battery was obvious. The Court relied upon the corollary principle that **when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious.**

KSR Intl. Co. v. Teleflex, Inc., 127 S. Ct. 1727, 1740 (2007).

As KSR reaffirmed the "teaching away doctrine," it is appropriate to consider the Federal Circuit's view that "references that teach away cannot serve to create a prima facie case of obviousness." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Another passage found in *In re Gurley* at 553 recites: "[a] reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. Because Schumacher teaches away from crystalline desloratadine polymorphic mixtures and because Applicants claim desloratadine crystalline polymorphic mixtures that Schumacher warns against, Applicants believe that a rejection of obviousness based on Schumacher is improper.

Schumacher does not disclose a process for preparing crystalline desloratadine mixtures

Applicants also note that Schumacher prepares crystalline desloratadine from a process that is fundamentally different from the process that Applicants utilize to obtain the presently claimed crystalline desloratadine. Schumacher obtained the desloratadine crystalline polymorphs by crystallizing desloratadine from a **single organic solvent** (see col. 4, ll. 23-41, col. 9, l. 63 – col. 12, l. 8). The Examiner's attention is directed to Schumacher's exemplified embodiments, which are summarized in the following Table.

Example	Citation (Col.: line(s))	Crystallization Solvent	Washing Solvent	Comment
1	9:63~10:21	methyl isobutyl ketone (MIBK)	MIBK	% Form I not specified
2	10:24-60	MIBK	MIBK	1st crystallization: crude material (% of I- to-II unknown). 2d crystallization: 100% of Form I
3-A	10:63~11:9	methanol	hexane	% Form I not specified
3-B	11:10-26	MIBK	MIBK	100% of Form I
4	11:28-46	ethyl acetate	hexane	100% of Form II
5	11:48~12:8	di-n-butyl ether	n/a	Crystalline solid contained 92% (\pm 5%) of Form II

In each one of these examples, crystalline desloratadine is obtained from a **single organic solvent** (MIBK, methanol, ethyl acetate, and di-n-butyl ether). Most of the examples where the polymorphic purity is specified (Examples 2, 3B, and 4), pure desloratadine having a single polymorph is obtained. In one example (Example 5), crystalline desloratadine Form II substantially free of Form I (92:8) is obtained. Therefore, Schumacher exemplifies that sometimes mixtures of polymorphs are obtained and sometimes mixtures of polymorphs are not obtained. Yet, Schumacher provides no guidance as to when mixtures of polymorphs are obtained or how to go about to obtain only mixtures of polymorphs. There is no mention in Schumacher on how to obtain mixtures of polymorphs all of the time or even how to prepare the presently claimed crystalline desloratadine polymorphic mixtures.

Applicants note that the presently exemplified crystallization process is one that serves to control kinetically the percentage of polymorphs that are obtained. In contrast, the Schumacher process is one where there is no control of the percentage of polymorphs that are obtained, i.e., the Schumacher process is a thermodynamic process. By thermodynamic process, Applicants note that a supersaturated solution is used to obtain crystalline material and that as crystallization occurs to form one or more polymorphs, the one or more polymorphs may then interconvert. In other words, the formation of a mixture of polymorphs, if at all, is accidental at best. Applicants direct the Examiner's attention to the Guillory article at pp. 188ff for a further discussion of the thermodynamic aspects of crystal growth (Guillory in "Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids" which appears as Chapter 5 in "Polymorphism in Pharmaceutical Solids" (1999), Harry G. Brittain, Ed., Marcel Dekker, Inc.).

Summary – Claimed invention as a whole is unobvious over Schumacher

In summary, then, Applicants note that the presently claimed composition / mixture recites a range for a desloratadine polymorphic mixture that does not "overlap" or "touch" with the polymorphic mixture ranges disclosed in Schumacher. Additionally, even if one were to consider that the ranges are "close enough," Applicants note that the properties of the claimed composition / mixture are unexpected in view of Schumacher. This is especially true when one considers that polymorphism is generally regarded as being unpredictable. Applicants believe that Schumacher expressly teaches away from the presently claimed compositions / mixtures. The *KSR Court* recently affirmed the "teaching away principle" and the Federal Circuit has indicated that "references that teach away cannot serve to create a prima facie case of obviousness." Schumacher does not disclose or suggest a process for preparing a crystalline desloratadine polymorphic mixture as presently claimed. Indeed, Applicants note that Schumacher does not disclose or suggest a process for preparing the claimed crystalline desloratadine polymorphic mixtures. In view of these considerations, Applicants believe that rejection of the claims in view of Schumacher is improper. Applicants kindly request that the Examiner acknowledge the same and withdraw the rejection based on claims 1, 15, 28-29, and all respective dependent claims.

Provisional Rejection based on 11/283,276

The provisional rejection of claims 1-13, 15-26, and 28-59 under the judicially created doctrine of obviousness-type double patenting over claims 21-24 of pending application 11/283,276 ("the '276 application") is respectfully traversed.

Claims 21-24, of the '276 application, are reproduced below:

21. A mixture of crystalline Form I and Form II of desloratadine, containing about 50 ppm to about 4000 ppm of any one of isobutyl acetate, n-heptane, n-hexane, ethyl acetate, butanol, isobutanol, toluene, chloroform and combinations thereof.

22. The mixture of claim 21, comprising about 35-82% desloratadine Form I and about 18-65% desloratadine Form II.

23. The mixture of claim 22, comprising about 55-82% desloratadine Form I and about 18-45% desloratadine Form II.

24. A pharmaceutical formulation comprising the mixture of claim 21.

Although it may be true that claim 21 of the '276 application is directed to crystalline desloratadine comprising a mixture of Form I and Form II, claim 21 of the '276 application also recites that the mixture comprises "about 50 ppm to about 4000 ppm of any one of isobutyl acetate, n-heptane, n-hexane, ethyl acetate, butanol, isobutanol, toluene, chloroform and combinations thereof." This should be contrasted with each of Claims 1, 15, 28, 29, 37, and 49, in which there is no requirement to have a crystalline mixture that comprises "about 50 ppm to about 4000 ppm of any one of isobutyl acetate, n-heptane, n-hexane, ethyl acetate, butanol, isobutanol, toluene, chloroform and combinations thereof."

Applicants kindly request that the Examiner withdraw this rejection.

Applicants concurrently filed with the present response a Request for Continued Examination and a Request for a Three-Month Extension of Time under 37 CFR 1.136(a) with an authorization to charge the requisite fee under 37 CFR 1.17(a)(3) to Applicants' representative Deposit Account 13-2725. If for any reason the Request is separated from the present response,

then Applicants authorize the Office to charge the above-noted Deposit Account to pay any necessary fees so as to maintain the pendency of the present application.

Applicants believe that the present application is now in a condition for allowance. In the event that the Examiner acknowledges the same, then Applicants kindly request rejoinder of withdrawn claims 14, 27, and 60.

In view of the remarks contained herein, Applicants respectfully request a Notice of Allowance. If the Examiner believes that a discussion would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.



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A handwritten signature in black ink, appearing to read "Daniel R. Evans". The signature is written in a cursive, flowing style.

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Date: **January 16, 2008**